

REMARKS

Claim 59 has been amended to more clearly set forth the metes and bounds of the claimed subject matter.

Claims similar to those now pending in this application were finally rejected in an Office Action mailed July 2, 2001 (the "Action") in connection with Application No. 09/294,453, the immediate parent of the present continuation application (the "Parent Application"). The applicants now traverse these rejections, to the extent that they might be reasserted against the pending claims, for the following reasons.

1. Claim Rejections Under 35 U.S.C. § 103(a) Over Gress, Granelli, and Fodor

In paragraph 9 of the Action, the Examiner rejected all independent and many dependent claims pending in the Parent Application over a combination of papers by Gress et al.¹ ("Gress") and Granelli-Piperno et al.² ("Granelli") in view of a patent by Fodor et al.³ ("Fodor").

Before directly addressing the cited references, the applicants review certain legal principles of obviousness that guide their interpretation.

¹ Gress et al., 1992, Hybridization fingerprinting of high-density cDNA-library arrays with cDNA pools derived from whole tissues, Mammalian Genome 3:609-619.

² Granelli-Piperno et al., 1986, Lymphokine and nonlymphokine mRNA levels on stimulated human T cells, J. Exp. Med. 163:922-937

³ U.S. Patent No. 5,800,992, issued September 1, 1998, by Fodor et al., titled METHOD OF DETECTING NUCLEIC ACIDS.

Certain legal principles of obviousness

The basic legal principles of obviousness are ably summarized in the M.P.E.P. §§ 2141-45, to which reference is made herein in its entirety (and to the cases cited therein). Certain portions from these sections are particularly relevant to the present Amendment.

First, the M.P.E.P. reminds that to establish a *prima facie* case of obviousness, three basic elements must be established.

- (i) The prior art reference (or references when combined) must teach or suggest all the claim limitations;
- (ii) There must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings; and
- (iii) There must be a reasonable expectation of success.⁴

These three elements must be established by a preponderance of the evidence of record.

Importantly, this evidence establishing obviousness must be objective.⁵ An unsupported or subjective assertion that, for example, "it would have been obvious to one of ordinary skill in the art to modify the references to reach the claimed invention" is simply not enough. Objective

⁴ M.P.E.P. 2100-97 (7th ed., rev. 1; Feb, 2000) (emphasis added) (and the cases cited therein).

⁵ The Court has stated that: [a]ssertions of technical facts in areas of esoteric technology must always be supported by citation to some reference work recognized as standard in the pertinent art and the appellant given, in the Patent Office, the opportunity to challenge the correctness of the assertion or the notoriety or repute of the cited reference. . . . Allegations concerning specific "knowledge" of the prior art, which might be peculiar to a particular art should also be supported and the appellant similarly given the opportunity to make a challenge. " *In re Pardo*, 684 F.2d 912, 917 (C.C.P.A. 1982) (citations omitted) (emphasis added); *see also* 37 C.F.R. § 1.104(d)(2).

support for such an asserted understanding of one or ordinary skill must be provided in the prosecution record.⁶

The M.P.E.P. further reminds us of the following basic principles underlying any obviousness determination:

When applying 35 U.S.C. 103, the following tenets of patent law must be adhered to:

- (A) The claimed invention must be considered as a whole;
- (B) The references must be considered as a whole and must suggest the desirability and thus the obviousness of making the combination;
- (C) The references must be viewed without the benefit of impermissible hindsight vision afforded by the claimed invention and
- (D) Reasonable expectation of success is the standard with which obviousness is determined.⁷

Therefore, the claimed invention must be considered as a whole. It is not enough for obviousness that one or more individual elements, even critical elements, be suggested by the prior art; rather the entire claimed combination arranged as claimed and for its intended function must be suggested by the prior art. Also, the teachings of the references must be considered as a whole. It is improper to extract assorted technical elements from the various references and

⁶ Also, a combination of references, to be proper, must be operative for the intended purpose. *See, e.g., Tec Air, Inc. v. Denso Manuf. Michigan, Inc.*, 192 F.3d 1353, 1360 (Fed. Cir. 1999) (If when combined, the references "would produce a seemingly inoperative device," then they teach away from their combination. *In re Spornoble*, 56 C.C.P.A. 823, 405 F.2d 578, 587, 160 U.S.P.Q. 237, 244 (1969); *see also In re Gordon*, 733 F.2d 900, 902, 221 USPQ 1125, 1127 (Fed. Cir.1984) (finding no suggestion to modify a prior art device where the modification would render the device inoperable for its intended purpose)).

⁷ M.P.E.P. 2100-90 (7th ed., rev. 1; Feb, 2000) (emphasis added) (and the cases cited therein).

put them to undisclosed uses in combinations never suggested or motivated.⁸ Bits and pieces of references cannot be selected and assembled to achieve a claimed invention in a manner contrary to each reference's overall teachings and purposes.

Even more important, in evaluating obviousness, the teachings of the application and subsequent developments in the art must be entirely disregarded, and the mind cast back to a time before application filing to view then known art as it would be viewed by one of ordinary skill at that time.⁹ Then a claimed invention can be obvious only if the art so understood, and with all such impermissible knowledge disregarded, suggests the elements of the invention, motivates the desirability of the claimed combination, and provides a reasonable expectation of its success.¹⁰ If it is only the application itself that objectively suggests the claimed combination, or if only subsequent developments demonstrate success, the invention is not obvious.

Now, in the following, it is respectfully submitted that the claims pending in the present application are properly patentable over the combination of Gress, Granelli, and Fodor cited in the Action because this combination, as properly considered in view of the above principles, does not teach all the claimed elements, provides no objective suggestion of the desirability of

⁸ "Furthermore, rejecting patents solely by finding prior art corollaries for the claimed elements would permit an examiner to use the claimed invention itself as a blueprint for piecing together elements in the prior art to defeat the patentability of the claimed invention. Such an approach would be 'an illogical and inappropriate process by which to determine patentability.'" *In re Rouffet*, 149 F3d 1350, 1357 (Fed. Cir. 1998) (citations omitted).

⁹ See, e.g., *In re Kotzab*, 217 F.3d 1365, 1369 (Fed. Cir. 2000).

¹⁰ "To prevent the use of hindsight based on the invention to defeat patentability of the invention, this court requires the examiner to show a motivation to combine the references that create the case of obviousness. In other words, the examiner must show reasons that the skilled artisan, confronted with the same problems as the inventor and with no knowledge of the claimed invention, would select the elements from the cited prior art references for combination in the manner claimed." *In re Rouffet*, at 1357 (emphasis added).

the claimed combination, nor suggest its likely success, all of which are required for a *prima facie* case of obviousness.

The references do not teach all elements of the pending claims

The elements of the independent claims (claims 38, 56, and 70) are discussed element-by-element in view of the three cited prior references, and it is concluded that this combination does not teach or suggest to one of ordinary skill in the art at the effective filing date of this application all the elements of any of these claims.

The first element of all the independent claims is as follows:

(a) detecting physical signals from a plurality of units ordered in a probe matrix by contacting the probe matrix with gene transcripts or cDNA derived from said living thing subjected to said stimulus, wherein each unit of the probe matrix confines a probe comprising a different pre-determined sequence of nucleotides, and wherein said sequence is hybridizable with an identified gene of said living thing, or with a transcript of the gene, or with cDNA derived from the gene,

Considering this element first in view of Gress, it is submitted that the Examiner's contention that this reference shows throughout "patterns of transcription" obtained by means of an array of cDNA probes is incorrect.¹¹ Applicants submit that Gress shows only the use of hybridization fingerprinting to select for purposes of sequencing those unknown cDNA clones from a cDNA library that are hybridizable to a plurality of tissues from one or more organisms. Hybridization fingerprinting hybridizes arrays of unknown cDNA clones from an uncharacterized cDNA library with cDNA pool probes extracted from various tissues of various organisms.

¹¹ The Action at page 4.

These cDNA clone arrays cannot be the recited probe matrices because they do not contain fragments of known and identified genes. But even if they were, because the cDNA pools, whether or not from stimulated organisms, are not necessarily from the same organism as are the cDNA probes, hybridization cannot necessarily identify a single known gene. Indeed, cDNA pools from stimulated organisms cannot be used, because Gress' method requires the results of different hybridization with different arrays be comparable.

Applicants further submit that Gress is only concerned with the arts of genomic mapping and sequencing, particularly with selecting desirable cDNA clones for sequencing. Because Gress never suggests any other application for the disclosed methods, this reference would not suggest to one of ordinary skill at that time any new methods of measuring gene expression at all.

Next, the Granelli reference also does not teach or suggest this detecting step because Northern blotting, this reference's principal tool, is plainly unrelated to the claimed probe matrices. Northern blots are entirely different from the recited probe matrices with a plurality of discrete units confining single probes to known and identified genes.

Moreover, whatever the nature of Granelli's blotting techniques, they cannot be fairly said to "detect" anything in the sense recited in this invention. The present invention has an essential quantitative and digital nature. Indeed, in one embodiment, the invention is a computer system that detects and transduces physical signals from probe matrices and then analyzes the transduced digital data in view of a database of similar data.¹² This nature is recited in the claims, which recite "detecting physical signals" in a quantitative form suitable for later

¹² See, e.g., Fig. 1; and page 4, lines 3-11.

"transducing," "storing in digital form," and ultimately "analyzing" by computer algorithms. The claims do not recite merely "merely observing" probe matrix hybridization.

No such "detecting" is disclosed by Granelli, because this reference is limited to observing Northern blot patterns by eye, and then visually comparing one image to another. The visual comparisons lead only to purely qualitative data which could not be used in this invention and is not recited in the claims. Further, Granelli never suggests that merely visual blot comparisons are problems needing solution, much less possible solutions. The only numeric-form data in this reference concerns protein abundance and activity; lack of numeric gene expression data is not a problem apparent from Granelli.

Lastly, Fodor also does not disclose or teach this first element of the independent claims. Applicants submit that Fodor's arrays include only oligonucleotides that, although of known sequence, are not specific to single, known genes. Hybridization of a sample to one of these arrays indicates the presence of complementary sequences, "features," in the sample, but none of these complementary sequence features necessarily indicates the presence or absence of any known gene, as does each unit in a probe matrix. Therefore, Fodor's oligonucleotide arrays cannot be the recited probe matrices.

Furthermore, Fodor suggests use of these arrays to generate "fingerprints," that is "feature" patterns for characterizing samples as similar or different. For example, if two cDNA clones have similar fingerprints, the clones are likely to map near each other, or to overlap; if two transcript samples from two tissues have similar fingerprints, then the tissues are likely to be at similar stages. Nothing more, for example concerning absolute position or identity, can be determined from such fingerprints. Therefore, fingerprint data from Fodor's arrays cannot be used for determining effects of a stimulus by expression analysis of an organism's gene transcripts as recited in the subsequent steps of this invention.

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1420 Fifth Avenue
Suite 2800
Seattle, Washington 98101
206.682.8100

Turning to the next elements recited in all independent claims, they are substantially identical to the next elements of claim 38, which recite:

- (b) transducing the physical signals into electrical output signals,
- (c) storing in digital form each electrical output signal in an output signal data structure, wherein each stored digital signal is associated (i) with said stimulus and (ii) with the identity of said identified gene,

Although Gress processes images of the array hybridizations into digital optical density (OD) values, this reference cannot store these OD values in the recited database. Particularly, the OD values cannot be stored in association with a stimulus and with a gene identity, because Gress does not know the identity of the gene carried in each cDNA clone, and also does not consider cDNA probe pools from organisms subject to a stimulus. Instead, the OD values are stored in association only with the name and location of the cDNA clone.¹³ Whether or not Fodor's fingerprint patterns are detected or transduced, Fodor like Gress cannot store any data as recited because none of Fodor's hybridization data provides information on single, known and identified genes, and Fodor never suggests samples derived from an organism subject to a stimulus.

Next, Granelli as already discussed provides only visual, qualitative Northern blot data, which is never detected or transduced for storage in digital or numeric form. Additionally, the applicants submit that Granelli does not disclose any database, much less a database with numeric data transduced from gene expression measurements. Granelli's table cannot be used in the subsequently recited computer implemented steps of this invention. Finally, this reference never suggests that a lack of quantitative data or an absence of computer data storage and

¹³ See Gress at pages 610-611 (section title "Image analysis").

analysis is a deficiency to be corrected, and does not motivate a person of ordinary skill to make improvements or modifications in the nature of this invention.

The remaining elements of each independent claims are now discussed claim-by-claim. The last element of claim 38 recites:

(d) analyzing the effect of said stimulus on said living thing by comparing the stored output signal data structure with an output signal data structure database, wherein the output signal data structure database comprises a plurality of output signal data structures stored in a computer memory.

It is plain that this element is not disclosed or suggested by the references. Neither Gress nor Fodor disclose or suggest data detected from the recited probe matrices, and certainly cannot propose any type of analysis of such unknown data. Because Granelli provides only visual, qualitative information on levels of a few mRNAs, this reference also does not disclose or suggest quantitative data detected from probe matrices, which is then transduced, stored, and analyzed in digital form by disclosed computer methods.¹⁴

In the Action, the Examiner has failed to explicitly consider this element. But establishing obviousness requires that the invention be considered as a whole, and the present invention not only encompasses making and using probe matrices by quantitatively detecting their physical signals, but also importantly analyzes this data by computer algorithms after it has been transduced digitally and stored in a computer database. For obviousness, all the recited elements must be taught by the prior art, and their recited combination objectively motivated by the prior art without any hindsight knowledge.

¹⁴ See, e.g., Figs 5-7; and page 15, line 24 to page 17, line 5.

Now considering the other independent claims, the last element of independent claim 56 recites forming an output signal data structure database by repeating the steps of detecting, transducing, and storing for gene transcripts derived from organisms subject to a variety of stimuli. Because quantitatively detected probe matrix data, much less databases of such data, is not taught by Gress, Granelli, or Fodor for the reasons immediately above, this last element is also not found in the cited prior art.

The last element of independent claim 70 recites comparing two sets quantitatively detected probe matrix data, a set derived from an organism subject to a stimulus and a set derived from the organism in a basal state. This element is also not taught by the cited references for the same reasons, namely, they do not disclose any such quantitatively detected probe matrix data.

In conclusion, it is respectfully submitted that the combination of Gress, Granelli, and Fodor do not teach all the elements of any of the independent claims. This combination particularly does not teach the first element of these claims, the recited probe matrices and quantitatively detected data from these matrices, nor does it teach the last element of the independent claims, database storage and computer analysis of this data.

Since such teaching is essential for establishing a *prima facie* case of obviousness, it is requested that the instant rejections be withdrawn without more.

The prior art provides no objective teaching to modify the references

In addition to teaching an invention's claimed elements individually, a *prima facie* case of obviousness requires that the prior art also objectively teach or motivate the desirability of the claimed combination and suggest that success of the combination is reasonably likely. These additional showings are not merely bothersome details; they are part of the essence of establishing obviousness.

LAW OFFICES OF
CHRISTENSEN O'CONNOR JOHNSON KINDNESS^{PC}
1420 Fifth Avenue
Suite 2800
Seattle, Washington 98101
206.682.8100

"The factual inquiry whether to combine references must be thorough and searching." It must be based on objective evidence of record. This precedent has been reinforced in myriad decisions, and cannot be dispensed with. . . . "Our case law makes clear that the best defense against the subtle but powerful attraction of a hindsight-based obviousness analysis is rigorous application of the requirement for a showing of the teaching or motivation to combine prior art references."¹⁵

And these showings must be based on objective teachings particularly pointed out by the Examiner.

The need for specificity pervades this authority. . . . "the examiner can satisfy the burden of showing obviousness of the combination "only by showing some objective teaching in the prior art or that knowledge generally available to one of ordinary skill in the art would lead that individual to combine the relevant teachings of the references".¹⁶

If these showing were not required, few inventions would be non-obvious, because a great majority of inventions (but not the present invention) are combinations of old elements already known in the prior art.¹⁷

Further all these teachings, especially the motivation to make the claimed invention, must be found in the art prior to the effective filing date of this application, without any consideration of the applicant's own specification or of knowledge of subsequent developments. It is submitted

¹⁵ *In re Lee*, 277 F.3d 1338, 1343 (Fed. Cir. 2002) (quoting *In re Dembiczak*, 175 F.3d 994, 999 (Fed.Cir.1999) abrogated on other grounds by *In re Gartside*, 203 F.3d 1305 (Fed. Cir. 2000)).

¹⁶ *Id.* (quoting *In re Fritch*, 972 F.2d 1260, 1265, 23 USPQ2d 1780, 1783 (Fed.Cir.1992)).

¹⁷ *In re Rouffet* at 1357.

that avoiding such impermissible hindsight is particularly difficult in connection with the present application, because at the present time "micro-arrays" have become an essential tool of biology, practically a commodity product, and the use of "micro-arrays" for expression analysis is now pervasive. It is difficult to understand the state of the art before these tools were known. Nevertheless, it must be done.

A critical step in analyzing the patentability of claims pursuant to section 103(a) is casting the mind back to the time of invention, to consider the thinking of one of ordinary skill in the art, guided only by the prior art references and the then-accepted wisdom in the field. Close adherence to this methodology is especially important in cases where the very ease with which the invention can be understood may prompt one "to fall victim to the insidious effect of a hindsight syndrome wherein that which only the invention taught is used against its teacher."¹⁸

Obviousness of the present invention must be viewed through the eyes of one of ordinary skill in the art prior to this application's effective filing date of August 9, 1995. The desirability of the claimed combination and a likelihood of its success may be found somehow in general knowledge of those of ordinary skill or in the cited references themselves. Applicants submit that there was no such general knowledge in the art prior to the effective filing date of this application that motivated the claimed invention and suggested its success. The Examiner has not contended to the contrary, and in the event of such future contentions, supporting evidence is respectfully requested, for example, by citation to a textbook, paper, or other written material.¹⁹

¹⁸ *In re Kotzab*, 217 F.3d 1365, 1369 (Fed. Cir. 2000).

¹⁹ See 37 C.F.R. § 104(d)(2).

At the very least, unsupported contentions about the content of the prior art which may be used to cobble together the present invention risk contamination by impermissible hindsight knowledge in a case such as this.

Turning now to the relevant teachings of the cited references, it is undisputed that there are no explicit teaching motivating the claimed invention and suggesting its likely success. Neither Gress nor Fodor, considered as a whole, is relevant to the problem addressed by the invention, namely the provision of improved methods for determining potentially genome-wide effects of a stimulus on an organism from gene transcripts derived from the organism. Gress only purports to advance the arts of genome mapping and sequencing by demonstrating how hybridization fingerprinting may be used to select cDNA clones for sequencing, a problem entirely unrelated to the present invention's problem. Although Fodor proposes many hypothetical uses of oligonucleotide arrays made by the disclosed *in situ*, light-directed synthesis method, including clone mapping and sequencing, they are all based on fingerprinting methods that cannot be used to detect the information recited in this invention. Accordingly, Fodor never once proposes generally applying the disclosed arrays to measure expression of known and identified genes, much less to solve the specific problem of this invention.

It is submitted that an ordinarily-skilled person prior to the effective filing date of this application might have combined Gress and Fodor, but only to solve the mapping and sequencing problems which both references explicitly address. One of ordinary skill in the art attempting to solve the problem addressed by this invention but having no knowledge of probe matrices or their use in expression measurement or of this invention would have found no useful teachings in either of these references. On the current record, the only suggestion to apply

LAW OFFICES OF
CHRISTENSEN O'CONNOR JOHNSON KINDNESSSMLLC
1420 Fifth Avenue
Suite 2800
Seattle, Washington 98101
206.682.8100

Fodor's oligonucleotide arrays to the problem of this invention is in this invention's own specification.²⁰

Granelli also provides no motivation to make this invention. This reference uses primarily Northern blotting along with seven nucleic acid probes to qualitatively study the levels of seven lymphokines and non-lymphokines.²¹ However, considered as a whole, Granelli never discusses any problems or inadequacies with Northern blotting; Granelli never indicates further work that might be possible with improved techniques. Accordingly, this reference simply does not motivate any improved expression measurement techniques, much less those of the claimed invention.

In conclusion, neither the cited prior art nor general knowledge in the art provides any objective motivation or suggestion of the desirability or success of the claimed invention. Therefore, it is only use of the applicants' own specification and subsequent developments, which is impermissible hindsight, that leads from the combination of Gress, Granelli, and Fodor to the claimed invention.

Finally, therefore, the applicants respectfully submit for these additional reasons that the combination Gress, Granelli, and Fodor references does not establish a *prima facie* case of obviousness of any independent claim, and withdrawal of the present rejections is courteously requested.

²⁰ See Specification at page 18, lines 15-17.

²¹ "The availability of a large number of DNA probes has made it possible to monitor the polyclonal stimulation of T cells at the level of specific mRNAs." This "large number" included a total of seven probes for IL-2, IFN, *c-myb*, *c-myc*, *c-fos*, HSP-70, and IL-2 receptor. Granelli at pages 929-930.

2. Claim Rejections Under 35 U.S.C. § 103(a) Over Gress, Granelli, Fodor, And Watson

In paragraph 10 of the Action, the Examiner rejected dependent claims reciting yeast cells that were pending in the Patent Application over the combination of Gress, Granelli, Fodor, and further in view of Watson et al. ("Watson"),²²

Briefly, the Watson reference includes two chapters from a well known, introductory textbook concerning the regulation of protein synthesis in bacteria and concerning yeasts as model eukaryotic organisms. Watson does disclose or suggest, *inter alia*, use of an ordered matrix of probes, each probe comprising a pre-determined nucleotide sequence hybridizable with an identified gene, or a transcript, or cDNA of the gene, or a database as recited by the claims.

Consequently, Watson cannot overcome the deficiencies in the combination of the Gress, Granelli, and Fodor references, and the combination of these reference with Watson asserted by the Examiner in the present rejections does not establish the *prima facie* obviousness of any claim. Withdrawal of the instant rejections is courteously requested.

3. Double Patenting Rejection

In paragraph 16 of the Action, the Examiner rejected certain claims under the judicially created doctrine of obviousness-type double patenting over U.S. Patent No. 5,777,888 in view of Fodor.

In response, upon an indication of allowable claims in the present application, the applicants intend to submit any necessary terminal disclaimers with respect to Patent No. 5,777,888.

²² Watson et al., 1987, *Molecular Biology of the Gene*, Benjamin/Cummings Publishing Co., Menlo Park, CA, Chaps. 16 and 18.

CONCLUSION

Applicants respectfully request entry of the foregoing remarks into the file of the above-captioned application. Applicants believe all the pending claims are in condition for allowance. Reconsideration and withdrawal of the Examiner's objection and rejections and allowance of the application are earnestly requested.

If any outstanding issues remain, the Examiner is invited to telephone the undersigned to discuss the same and to arrange for prompt and efficient handling of the above-captioned application.

Respectfully submitted,

CHRISTENSEN O'CONNOR
JOHNSON KINDNESS^{PLLC}



Barry F. McGurl
Registration No. 43,340
Direct Dial No. 206.695.1775

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CHRISTENSEN O'CONNOR JOHNSON KINDNESS^{PLLC}
1420 Fifth Avenue

Suite 2800
Seattle, Washington 98101
206.682.8100

VERSION WITH MARKINGS TO SHOW CHANGES MADE OCTOBER 31, 2002

In the Claims:

59 (Amended) The method of claim 56 wherein the probes comprise nucleotide sequences selected so as to be hybridizable with a transcript of one or more of the identified genes, or with cDNA derived from one or more of the identified genes.

67. (Amended) The method of claim [64]63, 64 or 65 wherein the living thing is a fungus.

68. (Amended) The method of claim [64]63, 64 or 65 wherein the living thing is a eukaryote.